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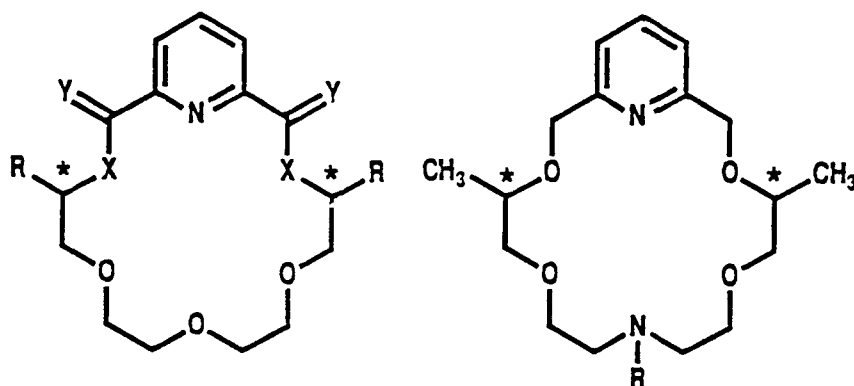
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19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>(4S,14S) - (+) -3,15-Dimethyl-4,14-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (compound 8 in Figure 1) undergoes significant conformational changes in solution as shown by changes in both its optical rotation in CHCl₃ and its ¹H NMR spectrum in CDCl₃. The solid state conformer has nearly C₂ symmetry. Two other conformers have been postulate by a computer modeling approach. These postulated conformers could cause the peak shifts noted in the ¹H NMR spectra.</p>			
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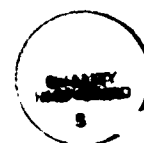
Figure 1. Chiral Diamido-, Dithionoamido-, Diaza- and Azapyridino-18-crown-6 Ligands



- | | |
|---|-----------------------------------|
| 1, X = NH; Y = O; R = benzyl (S,S) | 10, R = H (S,S) |
| 2, X = NH; Y = S; R = benzyl (S,S) | 11, R = C(O)CH ₃ (S,S) |
| 3, X = NH; Y = H ₂ ; R = benzyl (S,S) | |
| 4, X = NH; Y = O; R = phenyl (S,S) | |
| 5, X = NH; Y = S; R = phenyl (S,S) | |
| 6, X = NH; Y = H ₂ ; R = phenyl (S,S) | |
| 7, X = NCH ₃ ; Y = O; R = phenyl (S,S) | |
| 8, X = NCH ₃ ; Y = S; R = phenyl (S,S) | |
| 9, X = NCH ₃ ; Y = H ₂ ; R = phenyl (S,S) | |

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Dithionoamide ligand **8** exhibited a time-dependent optical rotation. The first measurement, taken after two minutes of dissolution of the crystals (recrystallized from ethanol), was $[\alpha]_D^{22} + 14.55$ ($c = 1.077$, CHCl_3). The optical rotation of this solution increased gradually and after 30 min. it was $+ 106.0^\circ$, after 40 min. $+ 110.4^\circ$, after 60 min. $+ 112.2^\circ$, and after 90 min. $+ 112.3^\circ$. The optical rotation of the solution was then checked daily for 2 weeks, but no additional changes were observed. When **8** was recovered from the chloroform solution and recrystallized from ethanol, the resulting crystalline **8** had the same optical rotation and mp as the original solid. A change was also noted in the ^1H NMR spectrum of **8**. The initial ^1H NMR spectrum of **8** in CDCl_3 was consistent with a compound having one conformation which is symmetric about the C_2 axis

of symmetry. As early as 2 min. after dissolving the crystals, new peaks appeared which can be attributed to a second, less symmetrical conformer. After 40 min (about the time equilibrium was established) the ^1H NMR spectrum indicated the presence of a third conformer as well. The starting conformer predominates as shown in Figure 5 which shows the ^1H NMR spectra at 2 min., 40 min., and 2 weeks. The X-ray crystallographic study showed two conformers in the unit cell, however, they are very similar and could not be distinguished in solution by ^1H NMR spectroscopy. Neither contained a C_2 axis though Figure 4 shows a pseudo two fold axis passing through the nitrogen atom of the pyridine and the opposite oxygen atom on the macroring. The original conformer(s) in the crystal remain the dominant species (50%-60%) in solution. The combination of the non-symmetrical conformers accounts for about 50% of the total concentration as determined by integration of the peaks assigned to the benzylic C-H protons and 40% integration of the N-methyl peaks. A minimum of three conformers is necessary to explain the three triplets observed for the pyridine hydrogen in position 4 ($\delta = 7.77, 7.69$ and 7.85) and the four N-methyl peaks ($\delta = 3.00, 3.11, 3.40$ and 3.42) observed at equilibrium. It is noteworthy that, similarly to the optical rotation results, there were no significant changes in the ^1H NMR spectrum after about 40 min (see Figure 5).

The optical rotation is a macroscopic measurement and is the result of isotropic motion averaging of all possible orientations of the chiral center. It is known that different conformers can have different optical rotations. In the case of compound 8, there are two identical chiral centers in each molecule. This means that the chiral centers isotropically tumble in pairs. In the symmetrical conformer,

this pairwise tumbling would be expected to yield a different optical rotation than if the chiral centers were tumbling independently. Similarly, in the two non-symmetrical conformers, the chiral centers tumble in pairs with distinctly different spatial relationships. The change in optical rotation with time can thus be attributed to the establishment of an equilibrium among three conformers.

The solid structure has two conformers varying only slightly. The C=S bonds are out of the plane of the pyridine ring and the planes of the phenyl rings are rotated about 90° from coplanarity with the neighboring C-H bonds (see Figure 4). Molecular modeling, using force field calculations, suggests that the C=S bonds would be coplanar with the pyridine ring when not in the solid state. Performing a simple energy minimization, using the x-ray coordinates as the starting point, produces a conformation with that very characteristic (Figure 6). The methyl groups are out of the macrocycle "average" plane and are no longer anti to the sulfurs as they are in the solid (Figure 4). One phenyl ring is approximately coplanar with the adjacent C-H bond deshielding this benzylic proton and shielding the neighboring macroring methylene protons. The other phenyl ring is not coplanar to the adjacent C-H bond and has the opposite shielding effect causing chemical shift splitting.

The low energy conformation of 8, derived from a grid search using force-field calculations, can be seen in Figure 7. In this conformer, the C=S bonds are approximately coplanar with the pyridine ring. The methyl groups are out of the plane of the macrocycle and are shielded by the C=S bonds and deshielded by the phenyl rings. The phenyl rings are approximately coplanar with the adjacent C-H bonds but are on the opposite side of the macroring from the neighboring

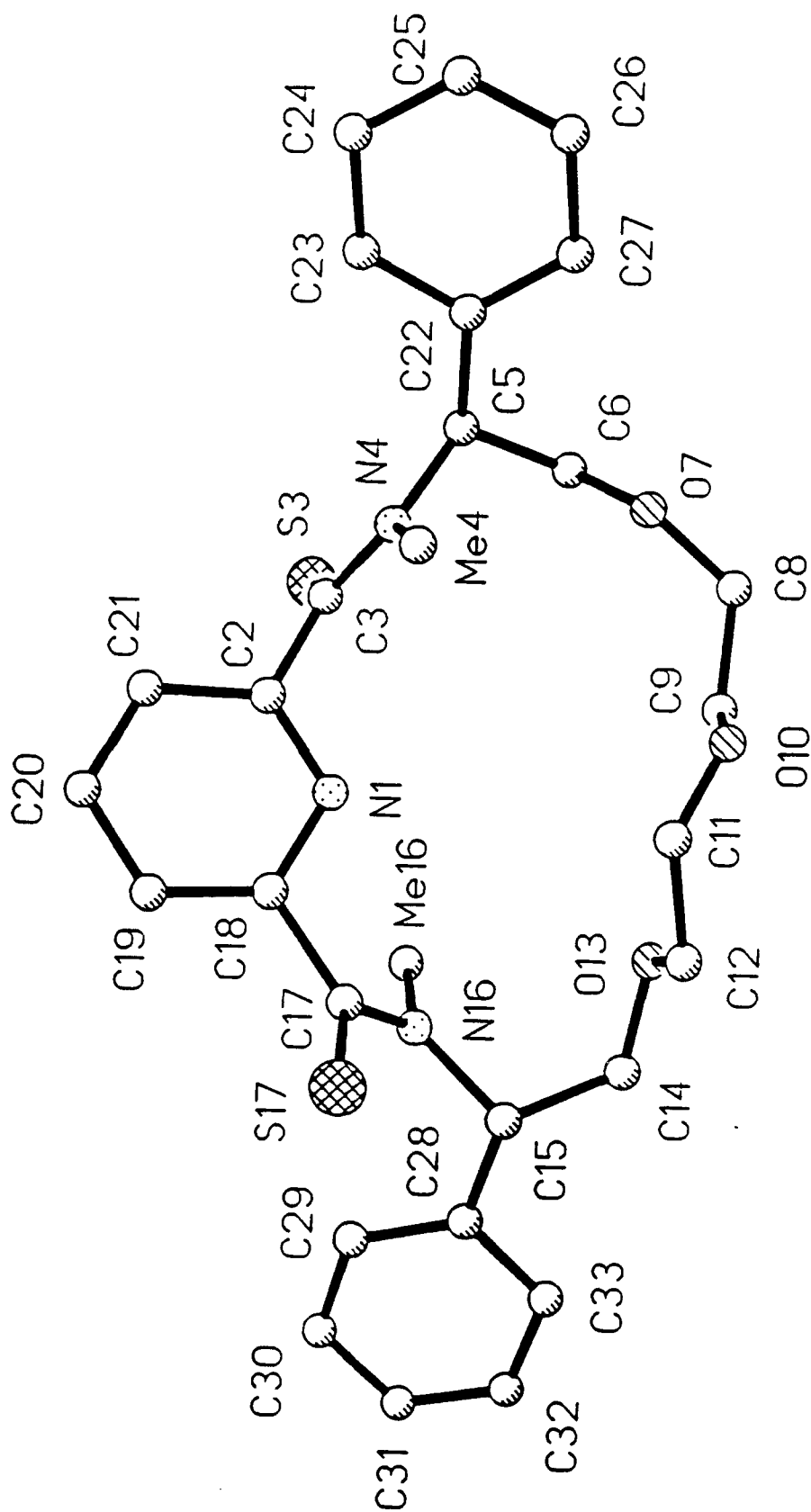
macroring methylene protons. Thus, those methylene protons are too far removed from the benzene rings to be affected.

The equilibrium NMR spectrum of 8 requires the presence of at least three conformers to explain the chemical shifts. The major component is the conformer exhibiting C_2 symmetry which is seen immediately upon dissolution of the crystals (conformer A) (Figure 4). The upfield movement (two triplets at $\delta = 5.34$ and 5.46) of the chemical shift of the benzylic proton which occurs after a short time is consistent with the molecular modeling conformer seen in Figure 6 (conformer B), and would be caused by a rotation that brings the C=S bonds to coplanarity with the pyridine ring and the consequent movement of the benzylic protons from the deshielding to the shielding region of the C=S double bond. Although these protons are still deshielded by the phenyl rings, one phenyl ring is rotated as described above and the C_2 symmetry is lost. The presence of conformer B would also explain two of the methyl shifts seen at equilibrium ($\delta = 3.11$ and 3.40). One of the methyl groups experiences an environment very similar (but not identical) to that in conformer A, while the other is substantially deshielded by rotation of its neighboring phenyl ring. The third methyl shift which is observed after several minutes must be attributed to the presence of a third conformer. The molecular modeling conformer seen in Figure 7 (conformer C) is consistent with that third methyl shift ($\delta = 3.42$) as the environments of the methyl groups are identical in this conformer and there is substantial deshielding by the phenyl rings. The two small triplets from the hydrogen at position 4 on the pyridine ring ($\delta = 7.69$ and 7.85) are also explained by the presence of conformers B and C, as is the additional doublet from the hydrogen at position 3 ($\delta = 7.60$). The upfield triplet observed within a few minutes is

consistent with conformer B. One C=S bond is rotated into close proximity with the proton at position 3 of the pyridine ring. This causes downfield movement of the chemical shift for the position 3 hydrogen due to deshielding by the C=S double bond and upfield movement of the chemical shift for the hydrogen at position 4 which is similar to the shielding which occurs at positions ortho to electron-withdrawing substituents on an aromatic ring. The other C=S bond is coplanar with the pyridine ring but is rotated away from the position 3 hydrogen and would thus not affect the pyridine ring protons. The position 4 hydrogen triplet at $\delta = 7.85$ as well as the position 3 doublet at $\delta = 7.60$ can be explained by conformer C. In this conformer both C=S bonds are coplanar with the pyridine ring and both are in close proximity to the position 3 hydrogen. The protons at position 3 experience the same deshielding, but now the position 4 hydrogen is also deshielded analogous to a proton ortho to two electron-withdrawing substituents.

Conformers A and B exhibit only small energy differences and therefore the equilibrium between them should be established rapidly. In the NMR spectra, the triplet at $\delta = 7.69$ appears early on, as do the methyl shifts at $\delta = 3.11$ and 3.42 . Conformer C is markedly different from the other two conformers which would indicate a higher energy barrier to form and thus a slower attainment of equilibrium. The triplet at $\delta = 7.85$ ppm is only present much later in the study. No energies are reported as all modeling was performed in the gas phase at 0°K , therefore no solvent effects are included. All of the conformers are consistent with the NMR data, but are not considered to be definitive. They are proposed only to suggest reasonable conformations and transitions that cause the time dependent changes seen in the NMR spectra.

Figure 4. X-ray crystal structure of the unprimed molecule of **8** drawn with SHELXTL-PLUS.³⁹ The primed molecule and hydrogen atoms were omitted for clarity.



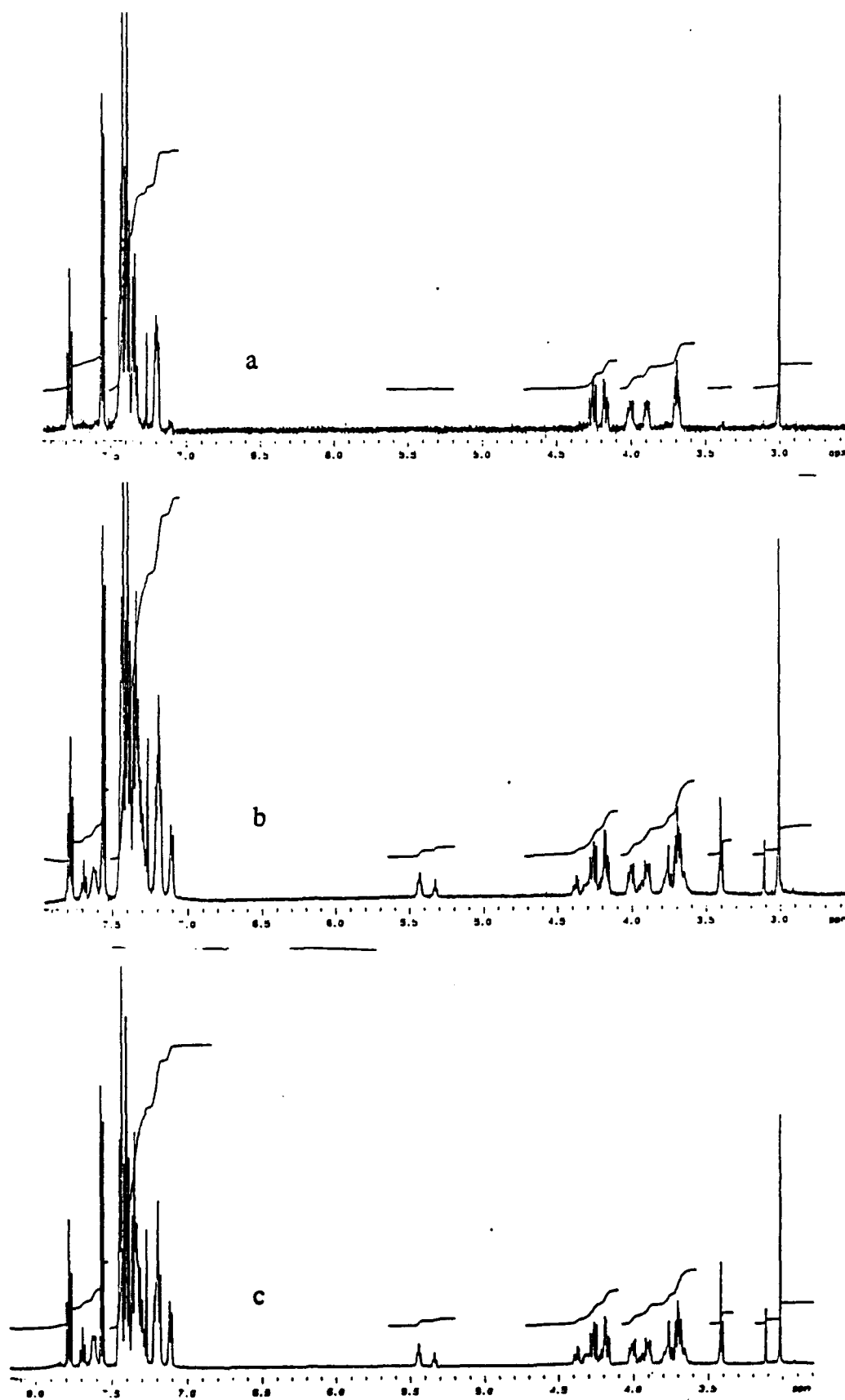


Figure 5. 500 MHz ¹H NMR spectra of **8** in CDCl₃: (a) after less than 2 minutes; (b) after 40 minutes; (c) after 2 weeks

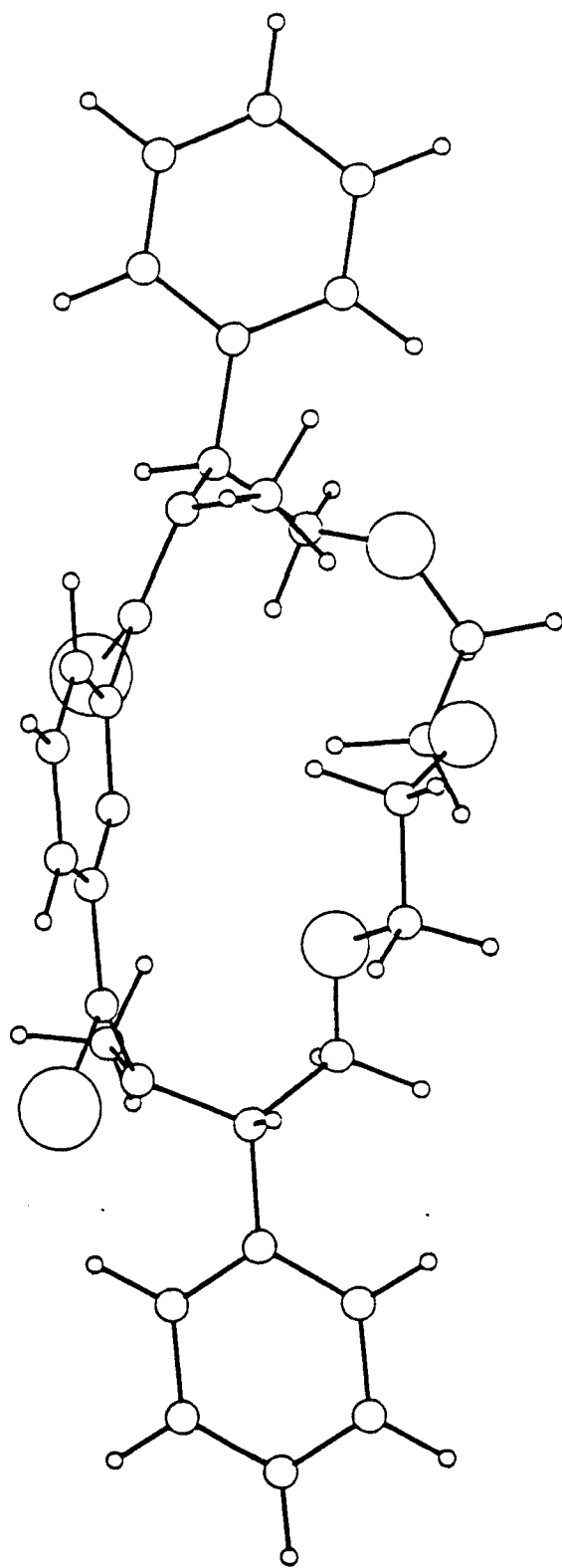


Figure 6. Force-field minimized structure of **8** using X-ray coordinates as the starting coordinates

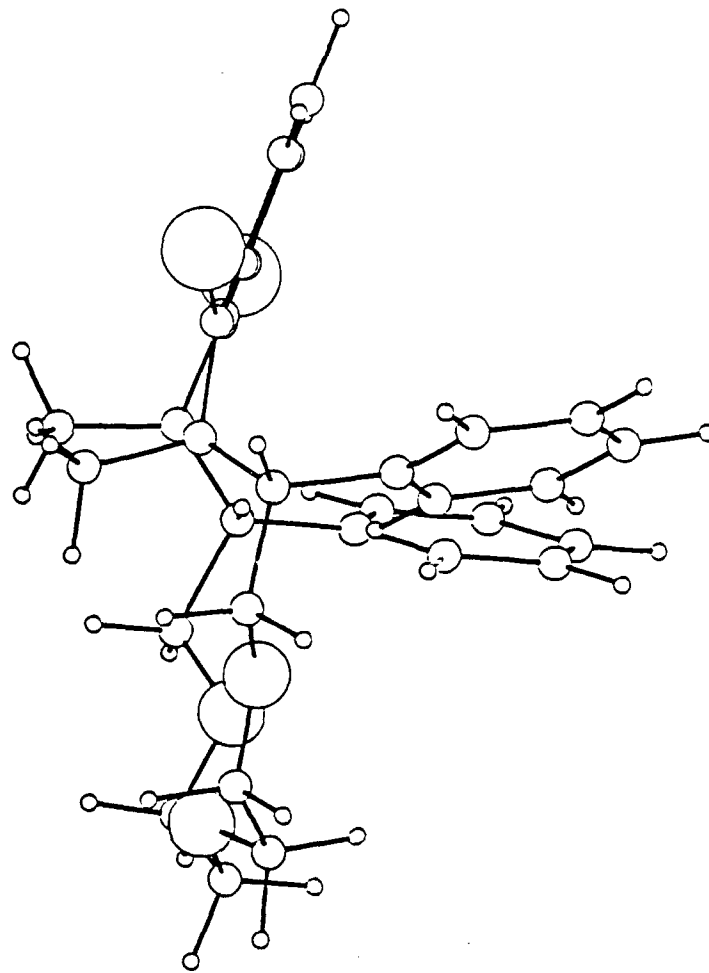


Figure 7. Low energy conformation of 8 from a grid search using force-field calculations